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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/463,904
Filing Date: June 05, 1995
Appellant(s): PHIPPS, JOSEPH B.

Ralph C. Francis
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 5, 2004 appealing from the Office action mailed June 19, 2002.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

The amendment after final rejection filed on June 19, 2003 has been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter as presented by appellant is substantially correct, but does not provide a concise explanation of the invention. The examiner believes the following statement will aid the Board as to the mechanics and issues of the device as they relate directly to the claims. The claimed invention is a method of delivering fentanyl salt by iontophoresis, wherein the fentanyl salt concentration is maintained above about 16 mM throughout the delivery period. Iontophoresis itself is a well known method of driving a charged drug (i.e. positive or negatively charged) into a patient wherein the charged drug is repelled by one of the positive or negative electrodes and attracted to the other electrode. The drug Fentanyl, which is in a free

base form, is not a sufficiently charged form of the drug and must be coverted to a charged form the drug, namely a fentanyl salt (i.e. fentanyl HCl or fentanyl citrate). The salt form dissolves in water so as to release the positive, protonated, fentanyl ion, which is the stored in a reservoir positioned adjacent the electrode used for delivery. The delivery of fentanyl salt by iontophoresis is also a known method, noting that appellant's claim 1 is in a Jepson format. The issue before the Board is related to Figure 2 of appellant's specification, which shows a curve for "normalized" flux, i.e. fentanyl salt delivered from a reservoir versus the concentration of fentanyl salt in the reservoir. The "normalized" flux curve being empirically determined by measuring the flux at each fentanyl salt concentration (at constant applied current and/or voltage) and dividing the resulting flux by the maximum flux that can be obtained empirically. Thus the maximum flux, i.e. 100% delivery rate, is shown to occur at about 6 mg/ml, which corresponds to 16 mM in the claims. Thus, the point on the curve wherein the normalized flux approaches 100% is the point wherein the flux becomes independent of presence of other ions, ions that are considered in the art to be "competitive" ions or "parasitic" ions. See page 25 lines 25-29 of applicant's specification. These competitive ions can naturally in water such as with hydrogen protons, metals etc. or alternatively can be added purposefully for a variety of reasons for instance to help stabilize the medicaments or gels. One major importance of having the drug concentration maintained above the concentration of maximum flux is that for a given amount of current applied, a given amount of drug will be delivered. Thus the amount of drug delivered is controllable and will not decrease as drug is depleted from the reservoir.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,171,294	Southam et al	1-2001
5,879,322	Lattin et al.	3-1999
5,423,739	Phipps et al.	6-1995
5,320,731	Muller et al.	6-1994
5,232,438	Theeuwes et al.	8-1993
5,273,768	Haak et al.	4-1993
5,125,894	Phipps et al.	6-1992
4,931,046	Newman	6-1990
4,588,580	Gale et al.	5-1986

Chapter 12, Iontophoresis, in Electrokinetischeskie kapillarnykh system: monographicheskie sbornik, Editor: Rebinder, Moskow USSR Academy of Science, 1956, pp. 310-327 - translation presented as pp. 1-31

Ashburn et al, "The Iontophoresis of Fentanyl Citrate in Humans", Anesthesiology, Volumne 82, no. 5, (May 5, 1995) ,pp 1146-1153.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1, 4, 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Phipps et al 5,423,739 in view of the combined teachings of Rebinder (Chapter 12, Iontophoresis, in Electrokinetischeskie kapillarnykh system: monographicheskie sbornik, Editor: Rebinder, Moskow USSR Academy of Science, 1956, pp. 1-31 of translation), Phipps 5,125,894 and Muller et al USPN 5,320,731.

Applicant's claim 1 is written in the form of a Jepson type claim wherein the preamble of the claim indicates that the delivery of fentanyl salt by iontophoresis is known and admitted prior art. Primary reference Phipps et al '739 likewise has the elements of this basic combination in teaching iontophoretic devices that use hydrogel layers which, when hydrated with an aqueous solvent (column 3 lines 40-44), will contain the drug in a protonated species as well as free chloride in the aqueous solution. In essence, the resulting composition contains a drug in its aqueous salt form as specified in the claims. The list of drugs included to be used in their salt form as medicaments include fentanyl (column 13 line 50). The hydrogels used in the iontophoretic devices may include the drug therein in either a single layer embodiment (column 3 lines 34-39) or a two layer embodiment with a hydrogel carrier layer and a hydrogel skin contact layer with an adhesive (column 6 lines 18-20). Thus, the use of fentanyl salts iontophoretically delivered to achieve an analgesic effect by way of

hydrogels containing aqueous solutions as reservoirs are established as was indicated in the use of the jepson format in appellant's claim 1.

While the delivery of fentanyl salts by iontophoresis was well known at the time of appellant's invention, Phipps '739, like others, fail to specify the particulars of the drug concentration as defined in appellant's claimed invention. Specifically, the prior art of record fails to specify when using the drug fentanyl, the drug concentration is maintained at a concentration above about 16 mM such that the concentration of fentanyl salt in the drug delivery reservoir is maintained at a concentration level at which the flux of the drug is independent of concentration. As noted in the summary of the invention as stated above in the examiner's amendment, from figure 2 of appellant's specification, the drug delivery rate for fentanyl, when graphed as a normalized flux versus concentration, becomes independent of concentration at a value above 16 mM (6 mg/ml Fentanyl HCl) such that for a given level of applied current, variations in drug concentrations will not vary the drug delivery rate, provided that the drug concentration remains above the threshold level.

While Phipps '739 and others were silent with respect to the concentrations of Fentanyl that is used to achieve analgesic effects, the generalized principle of testing known drugs to determine their optimal conditions, especially that of concentration, forms the cornerstone of modern pharmacology and would have been obvious to anyone of any skill in the art who had read the Phipp's '739 disclosure. The requirement to test the fentanyl in the hydrogel reservoirs to determine the optimum conditions of operation to which achieve analgesia wherein relief is achieved in the minimal time and

in the most efficient manner would be apparent. Moreover, those of ordinary skill in art of iontophoretic delivery, would have been even more so motivated to have performed the same tests as appellant to have so as to determine the useful amounts of Fentanyl. The Rebinder reference dated 1956, which has been cited on several USPN patents owned by the former assignee as the current appellant, discusses the phenomena that is exhibited in applicant's figure 2, that is the relationship between medicament ion concentrations and "competitive" or "parasitic" ion concentrations. The reference also demonstrates the recognition of testing necessary for every drug to determine appropriate. The commonly owned Phipps patent '839 discusses the idea of using drug concentration ions above threshold values thereby making certain that a linear relationship exists between current and the drug delivered such that the amount of drug delivered is predictable , i.e. when x amount of current is delivered, y amount of drug is delivered. Muller '731 patent is cited for making similar points in the recognition that excessive amounts of drugs are necessary so as to delivery the amount desired as well as conserve battery power by optimizing delivery efficiency.

Specifically the Rebinder, U.S.S.R Academy of Science pp 310-327 reference provides one of the earlier teachings concerning the problems of parasitic ions (a.k.a. competing ions) and their effect upon drug delivery efficiency. Parasitic ions, such as hydrogen ions are always present in aqueous solutions although there concentrations can be adjusted by adjusting parameters such as pH. The Rebinder reference is dated 1956 and has been cited in several reexam proceedings as well as patents prior to appellant's filing date, and obviously available to the public at large. The Rebinder

reference is concerned with the relationship between drug concentrations and drug delivery efficiency and the inconsistencies observed in past observations regarding complex ion concentration (i.e. large molecules) versus simple ions and there dependence of concentration for tissue introduction.

> Published experimental data on this question are inconsistent. On one hand, qualitative clinical observations suggest that under the conditions of clinical practice, the higher the concentration of the initial solution , the greater the therapeutic effect. These data are largely based on the iontophoresis of complex organic ions. On the other hand, the quantitative data of Schafferstein (1939) show that for a number of simple ions, tenfold changes in the concentration of a substance have practically no effect on the amount introduced within the limits of experimental error.

Later, in experiments on model membranes, Rebinder notes that for the drugs and membranes used the amount of drug delivered is independent of concentration, however the presence of parasitic ions, in sufficient amounts relative to the major ion, may reduce the efficiency of the major ion delivery:

> The results obtained in the experiments in which "parasitical"ions K^+ (C^0_{KCl}) were added to the external dye solution (series Ia, Ib, IIIa, and IIIb) require no explanation. A small amount of KCl (.001N) added to a solution with a high concentration of the dye(IIIa) had no effect onp/q, while the same addition to a dilute solution (series Ia) led to a reduction in the amount of the major ion introduced.
>
> The amount of major ion introduced (p/q) falls off sharply both with an increase in the concentration of the parasitic ion (series I->Ia->Ib) and with a decrease in the concentration of the major ion (series IIIb ->Ib), i.e., in all cases in which the relative amount of the major ion in the solution was reduced.

This statement parallels the statement found on page 25 lines 25-27 of appellant's specification and demonstrates the same effects found in appellant's figure 2.

Similar results and conclusions were reached for in vivo studies. Rebinder then tries to resolve the differences observed experimentally versus those observed

clinically. Rebinder discusses the significance of parasitic ions as well as complex organic ions

> The following question is of importance in physiotherapeutic practice: how can these experimental results, which also have a theoretical explanation, be squared with the increase in the therapeutic observed with increasing concentration of the external solution.
>
> The most important reason for the discrepancy is apparently that during clinical practice, when a pad is used, parasitic ions undergo iontophoresis along with the major ions.
>
> It is perfectly clear that in the presence of parasitic ions, the medicinal substance will be introduced in smaller amounts than shown in Tables 120-122, and the lower the concentration of the solution, the less introduced.
>
> Physicochemical research is not yet capable of evaluating the conviction of physicians that higher concentrations of a medicinal solution provide a greater therapeutic effect. Since this view is based on observations made on the iontophoresis of complex organic substances, questions as to the diffusion of these substances through the skin and the formation of association complexes in the solution arise.
>
> With increasing concentration of solutions (higher than .1M, i.e., 3-4%) of complex organic substances it becomes necessary to take into consideration the possibility of association complexes forming, i.e., with the transition from a solution of a "colloidal electrolyte," as occurs, for instance dyes. In this case the process of iontophoresis becomes one of electrophoresis, and the amount of substance introduced may increase due to the increase in mass of the ion, since the linear mobility of colloidal particles is usually close to that of organic ions ($=2x10^{-4}$ cm/s). Nor should we forget the possibility of the reverse effect, namely, the decrease in the transport number in the skin as the particle size increases. The problem of how these effects are inter-related and the question of whether it is possible for association complexes to form in solutions of medicinal substances used for iontophoresis remain unresolved and require further research.

It is clear as far back as 1956 that the concepts that: 1) for concentrations regarded as normal working concentrations, iontophoresis for simple ions is independent of concentration 2) the relative

amount of parasitic ions to major ions effects the delivery rate of simple as well as complex ions 3) the delivery of complex organic ions may involve other factors and generally produce a fall off as there ratio of major ions to parasitic ions (i.e. complex ion concentration) gets smaller, and most importantly, 4) further research to discover the relationship between concentration and drug delivery for the various complex ions is desired. The mere testing of a particular ion for its dependence on concentration was readily apparent to those of ordinary skill in the art.

More recent than Rebinder are the teachings of Phipps et al USPN 5,125,894. Phipps et al discusses the relationships between drug delivery rates and drug concentration in general and how medicaments have a threshold level, above which a linear relationship exists between current levels and the amount of drug delivered. See Phipps '894 at column 10 line 41 to column 11 line16. In particular the reference states:

> In general, the amount of transport which occurs as a result of applied voltage is directly proportional to the amount of current passing through the cell. Thus, in general, if the amount of current is doubled, the rate of transport due to the electromotive force is also doubled;"

Later Phipps states:

> In practice, then, the amount of current can be utilized to control the rate of drug delivery. This can generally be done in either or both of two manners: change in the potential (voltage) applied between the active and ground electrodes; or, change in resistance to passage of current between the two electrodes. In practice, typically resistance to ionic conduction between the two electrodes decreases, as the electrolytic material begins to permeate the skin. That is, in practice there is observed a lower resistance to current passing between the electrodes, with the passage of time. Thus, over a sustained period of time, for a typical iontophoretic system with little or no extraneous ions, constant rate of target ion delivery or transport can be maintained with a lowering of voltage, at least over a given range of concentrations of drug ion in the active reservoir, when the concentration is not modified greatly and is above a threshold

level determined by physical/chemical properties of the transported species and tissue through which transport occurs.

Phipps further states:

In general, although rate of drug delivery is proportional to current, at a constant current, the rate of drug delivery (Rd) is independent of drug concentration (i.e. target species concentration) in the active electrode reservoir, provided that the concentration is at least above a threshold level (and little or no extraneous ions are present)

Phipps '894 dedicates the patent to various types of operation based upon these principles so as to make the drug delivery process more predictable. Its teachings are based upon those principles found in the earlier teachings of Rebinder. It is clear from the Phipps et al '894 disclosure that drug delivery predictability is essential for achieving success and that the determination, use and maintenance of drug concentration levels above a threshold levels for achieving predictability of delivery was well known. It is also apparent that the threshold levels for various drugs will vary from species to species. Therefore to have tested, determined and used the threshold levels for Fentanyl and applied them to an known iontophoretic system such as that of Phipps et al '894 whether or not added intentionally added extraneous ions are present would have been an obvious optimization of parameters to those of ordinary skill in the art to sustain desired levels of drug flux. .

In further support of the examiner's contention that is was known to use excess quantities of medicaments within the drug reservoirs and specifically to do so as to

increase the efficiency of delivery and avoid excessive energy expenditure the examiner cites Muller et al. USPN 5,320,731 patent. Specifically at column 3 line 50 it is stated:

> If the reservoir element held, at the start of the operation, only a quantity of active principle equal to the given total quantity of active principle to be administered, and if the current was passed until this quantity had entirely diffused through the skin of the subject, the said current, towards the end of the operation, would act above all to transport ions other than those of the active principle, which would lead to excessive energy consumption and long treatment times. It is therefore preferable, in order to avoid the above drawbacks, for the quantity of active principle present in the reservoir element at the start of the operation to be in excess with respect to the said given total quantity, the said excess being able, for example, to be from approximately 2% to 1000% and more specifically from approximately 2% to 500% of this given total quantity.

From the above passage above it is clear that others recognized the benefit of starting with drug amounts in excess of up to 1000 % (10 fold) that to be delivered so as to 1) prevent competitive ions other than the drug from becoming the principle ion being transported in the late stages of drug delivery and 2) avoid expending and wasting of excess battery energy in order to deliver the amount of drug desired.

Thus, it is apparent that the prior art recognized that it was important to be able to predict the amount of drug delivered per coulombs applied and that one must experiment using the particular drug be delivered to determine it properties. It was also known at the time of applicant's invention that in order to deliver a desired quantity of medicament to a patent, excess quantities must be provided so as to negate the effects of competing ions since efficiency decreases as drug delivery ions are depleted in the reservoir. It was also recognized that a threshold value exists wherein the effects of competing ions are no longer felt and that the amount of drug delivered become strictly

dependent on the amount of current applied. Given these facts as demonstrated in the prior art and taking into consideration that Phipps '739 recognizes that Fentanyl may be delivered to the body in aqueous salt forms, it would have been obvious at the time of applicant's claimed invention to use Fentanyl in an iontophoresis patch and to perform the routine testing of determining the most safe and effective concentrations of drug in the reservoirs to achieve patient analgesia.

2. Claims 1, 4, 7-9 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Haak et al USPN 5,203,768 (in view of the collective teachings of Rebinder, Phipps USPN 5,125,894 and Muller et al USPN 5,320,731 or in view of Newman USPN 4,931,046). Haak et al provides working examples of fentanyl in a hydrogels which are stated to provide 25 ug of fentanyl every 5 minutes that the device is in activation. The device is designed with an on off switch or a controller that automatically turns the device on and off as the pain medicament is needed (column 10 lines 44-54) or may be on a timer so that a known amount (column 14 lines 20-23) is delivered each time it is activated. One on-off cycle meets the claim language if the device stays above the 16mM concentration. Haak et al teaches that a predetermined constant level of current delivers the drug at a constant rate (column 10 line 54 -59). As shown in figure 2 of appellant's drawings, if drug is provided at a concentration below the threshold level, drug being delivered will constantly deplete the reservoir shifting the curve further and further to the right and thus decreasing it's efficiency. Since the device as stated in Haak patent, which was

commonly own by the Alza corporation at the time of the filing of the current application, is described as acting in a linear fashion every time the device is activated, for Haak to make this statement, it is inherent that the concentration is in the range claimed by applicant, namely above the required threshold level. Otherwise, the device would deliver less than the stated amount for each subsequent interval since the reservoir would be depleted and the efficiency would continue to decrease delivering less drug per interval as time goes by. In further support of the argument of inherency it is noted that Haak et al uses a 10% by weight concentration of Fentanyl in the hydrogel matrix to form the patch reservoir to which an aqueous solution (column 13 line 68 to column 14 line 1) is added. Thus, even if the gel, when hydrated, absorbs 4 times its weight in water, the concentration of Fentanyl will still be 2% of the solution in the gel and still more concentrated than applicant's gel of example 1, and three times the minimal concentration requirements of claim 1. Example 1 of this application has a concentration of 21 mg/ml of Fentanyl hydrochloride. Since applicant appears to have a common assignee and have access to these gels the examiner has in the past requested hydration data and other related material that may provide information about the drug concentrations in these examples. Haak teaches that the device is turned on during episodes of pain (i.e. turned on and off), thus a "substantial" portion of the drug remains in the reservoir when the device is intermittently turned off.

If not inherent, it would have been obvious in view of the collective teachings of Rebinder, Phipps '894 and Muller et al for reasons explained in the earlier rejection of claims 1, 4, 7-9 under Phipps et al '739 in view of the combined teachings of Rebinder,

Phipps '894 and Muller et al USPN 5,320,731. To have operated the device in the linear region for Fentanyl which would inherently include applicant's claimed range.

Alternatively, it would have been obvious in view of Newman USPN 4,931,046 to have placed as much drug as desired into the Haak et al. device and limit the amount delivered by a control circuit so that the patient may undergo self treatment for days on end as in the teaching of Newman. Starting at column 7 line 47, Newman describes a system in which pain killing drugs, which Fentanyl is considered amongst, are placed in an iontophoretic system which maybe patient controlled so as to let subsequent deliveries be administered by the patient but prevent over dosages. To have implemented such a system with the Newman teachings device would mean providing high concentrations fentanyl so as to provide multiple dosages of pain killing medication in a manner that assures a given amount of current delivers a given amount of drug as was long recognized as a requirement.

3. Claims 1, 4, 7-9 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the claims of Theeuwes et al USPN 5,232,438 (alone or further in view of the collective teachings of Rebinder, Phipps '894 and Muller et al USPN 5,320,731 or in view of Newman).

The claims of Theeuwes et al USPN 5,232,438 recite a device and a method for inducing analgesia in a patient using Fentanyl salt. The examiner considers the recited concentrations in the applicant's pending claims to be inherent in the Theeuwes et al claims, for had the reservoir contained an concentration less than the requisite 16 mM,

the amount actually delivered would have been less than Theeuwes et al calculated and the results of the claimed invention would have not been yielded. Although the specification of Theeuwes provides little information for such a method and device as opposed to the claims, the examiner still considers it inherent. Alternatively, it would have been apparent to one of ordinary skill in the art, that for such a device and method to be accomplished one would have tested various concentrations of fentanyl salts to achieve the greatest efficiency and safely according to the baisic principles of the collective teachings of Rebinder, Phipps '894 and Muller et al USPN 5,320,731

Alternatively, it would have been obvious in view of Newman to have placed as much drug as desired into the Theeuwes device and limit the amount delivered by a control circuit so that the patient may undergo self treatment for days on end.

Double Patenting

4. Claims 1, 4, 7-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,171,294. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of the current application recites a method of drug delivery where in the concentration is maintained above about 16 mM which from appellant's specification is a composition that comprises about 1-2% fentanyl (see appellant's specification page 29) which is also the same composition as claim 7 of the 6,171,294 patent. Therefore claim 1 of the current application is merely a broader version of claim 1 of the '294 patent with the intended dosaging schemes of

claim 1 of the '294 patent deleted but requiring similar concentrations. Moreover, the patent claims recite that enough fentanyl is supplied to the patch to provide for an each amount of drug delivered to be equal over a each equal time period of 20 minutes. Due to the fact that equal amounts of Fentanyl are delivered for the same amount of current applied for each dose up to 100 dosages, the patch must contain and maintain a Fentanyl Salt concentration amount that is about 16 mM Fentanyl salt during each of these time periods.

Response to Arguments

1. Rebuttal to Arguments/Evidence/Affidavits presented in the Appeal Brief - Summary of the Invention

A. Back ground -Toxicity arguments

The examiner notes that in the Appeal Brief Summary, under the heading of Background, appellant discusses his evidence ,namely the Yerasi and Edinboro references well as the Phipps declaration. As noted in the argument section of the final rejection mailed 6-19-2002, the Yerasi and Edinboro are directed to toxicity issues surrounding Fentanyl free base form of the drug, and not Fentanyl salts. The free base form has different absorption properties through the than Fentanyl Salts.

Despite the examiner's adressment and rebuttal of these evidentiary documents appellant still presents the potential toxicity problems of Fentanyl free base as evidence of nonobviousness and refers to the Yerasi and Edinboro references as evidence as well as the Phipps declaration. Each of the references deal with the problems of toxicity

in passive Fentanyl (free base) patches and not of Fentanyl salt. There is a distinct difference between the two in terms of their properties and it was known by appellant at the time of the filing of the present application. The arguments presented by examiner remain unrebutted at this time. The examiner herein repeats a portion of those arguments from the final rejectiondemonstrating that the allegations made by the appellant are unsupported by the facts. Notwithstanding, the examiner's references teach designing iontophoresis patches to prevent under dosing and over dosaing whereas appellant's claims provide no such protections

In regard to appellants statements as well as the Phipps declaration regarding toxicity issues, appellant states that because Fentanyl is a potent drug, one would not have used the high concentrations recited in the claims for iontophoretic delivery. However, appellant offers no *relevant* evidence to support his allegations. To the contrary, the evidence submitted by appellant would seem support the examiner's position rather then refute it. The fact is that the each of the references used by the examiner in rejecting applicant's claims provide more structure for preventing overdosing, rate limiting membranes in the case for Theeuwes and control circuits for Newman, and teachings directed towards limiting the delivery rate as well as the amount delivered. In contrast, applicant's claims (and specification) are devoid of any such corresponding structures. Even more ironic is that applicant provides no upper boundary for the concentration limit in their claimed invention. Toxicity, in terms of the amount of Fentanyl salt concentration in the reservoir is not an issue if one takes into consideration what the combination of references teaches. In support of his contention,

appellant has submitted two pieces of evidence, namely the Yerasi and Edinboro references. However these do not provide any such relevant teachings that would instruct those in the field of iontophoretic regarding the delivery of fentanyl salts. The Yerasi and Edinboro references are drawn to the *passive delivery of fentanyl in its free base form* while the current invention is directed to iontophoretic delivery of fentanyl in its various salt forms. The free base form will diffuse through the skin upon touching it, the salt forms will not. Appellant apparently alleges that the fentanyl salt would be delivered into the patients skin in a similar fashion as by passive diffusion which would ultimately lead to over dosages of the patients as in the two references cited by applicant. . However, as was well known to those in the art at the time of appellant's invention fentanyl salts are not readily diffusible through the skin at all and would not incur the same problems as the passive delivery patches. In fact, the Alza corporation, who is the assignees of the current application when filed, are well aware of their own patent of Gale et al USPN 4,588,580 and it's evaluation of fentanyl citrate salt permeability to the skin. Column 3 lines 10-15 states:

> We have discovered that fentanyl citrate, the form in which fentanyl is presently administered, has such a low skin permeability that it is not at all suitable for transdermal delivery even with the use of permeation enhancers. Instead we have found that, in order to obtain the delivery rates noted above, the drug should be incorporated in the transdermal therapeutic system in the form of the base.

The salt forms of fentanyl will only be delivered when current is applied, making it a very controllable medicament in iontophoresis.

Other researchers have made similar observations. Consider Ashburn et al "The iontophoresis of Fentanyl Citrate in Humans". This research paper appears to the first to

describe the actual delivery of a salt form of fentanyl in *in vivo* experiments. It is noted that Ashburn uses concentrations of 3 mg/ml (see page 1147) and actually conducts experiments to determine the amount drug that is delivered by passive modes. On page 148 it is stated:

> Plasma fentanyl concentrations for each study group are shown in figures 2-7. No fentanyl was detected after passive (0.0-mA) fentanyl delivery, indicating that there was no passive drug delivery with the delivery time used in this study.

Thus, the overdosages that occurred in the references cited by appellant are unlikely to occur had the references reservoir contents been Fentanyl salts as opposed to Fentanyl free base. Fentanyl free base is dangerous because the material can readily diffues through the skin. Furthermore, it is unclear as to exactly where in the text of the Yerasi and Edinboro references, that appellant finds their "conventional wisdom" that one of ordinary skill in the art would use low concentrations of fentanyl salt or for that matter fentanyl free base.. The text teaches nothing concerning limiting reservoir concentrations to any particular level but instead instructs the reader "To prevent fentanyl toxicity, both patient and care giver must be properly instructed on the use and hazards of fentanyl patches" (Edinboro et al page 742 -see Discussion). Wouldn't a physician teach a patient how to use an iontophoresis patch as well to eliminate potential hazards? In fact, the reference appears to be more supportive of the examiner's position and seems to directly oppose those statements made in the Phipps declaration. The Edinboro reference describes patches that use 10 mg of fentanyl free base therein to deliver fentanyl at 100 ug/ml. The examiner further notes that Gale et al USPN 4,588,580 use concentrations of 14.7 mg/g of Fentanyl in ethanol and water to

fabricate similar gels. Additionally, concern is expressed in the references that after the gels have been used they must be properly disposed of because of remaining Fentanyl in the patch. Appellant states that one skilled in the art (page 12 of the brief dated 3-2-199 lines 4-8) that "those of ordinary skill in the art would be led to using low concentrations of Fentanyl in the donor reservoir and to attempting to completely deplete the donor reservoir of Fentanyl at the conclusion of the total drug delivery period". In reality, nothing could be further from the truth, the prior art shows gel loadings that last for several days and recognize that the extraction of all of the drug from the gel would be an exercise in futility since as the drug is depleted from the reservoir the concentrations eventually become so low as to be useless. See Gale USPN 4,588,580 column 7 lines 65+. "The systems originally contained approximately 200 ug/cm^2 of Fentanyl and over the 24 hour useful life delivered approximately 50 ug/cm^2 resulting in a delivery of approximately 25% of the original drug loading". **In other words 75% of the drug loaded is never delivered.**

Even the Alza corporations own commonly assigned patent to Lattin et al USPN 5,879,322 recognizes that drug is frequently leftover in the reservoir after an iontophoretic delivery takes place. The claims, in particular claims 1 and 7, are directed to a method of folding a patch containing potent narcotic (the specification identifies fentanyl as such a narcotic) so as to avoid contact with the skin.(See column 3 lines 62-65) Obviously, those skilled in the art did not possess the same "conventional wisdom' as that argued by Phipps in the declaration of 8-3-98 that stated one would have completely depleted the patch of all drug.

The examiner does not understand how applicant justifies their allegations that others would have limited their concentrations while appellant shows no concern for such in their claimed invention. The evidence provided and accompanying arguments are deemed wholly unpersuasive.

C. The Phipps declarations.

The Phipps declarations are filed by the inventor of the current application himself and are consider to be mostly self-serving and rely's upon unsubstantiated allegations. The declarations were submitted to refute the examiner's reliance on the use of the '894 patent, which also lists Phipps as an inventor. The first Phipps declaration (appendix D of the brief) was offer an explanation to the passages relied upon by the examiner to demonstrate that threshold values exist for drugs concentrations and must be overcome to establish the linear relationship necessary for predictability. See the relevant quotations as stated above on pages 10-11 on this examiner's answer. The first declaration does not directly address the passages. The first declaration instead alleges that the toxicity of fentanyl and its permeability through the skin lead would have lead researchers to use low concentrations to minimize passive diffusion. This is of course, has been rebutted above by showing assignee Alza knew that Fentanyl citrate has very low skin permeability. See quote from Gale USPN 4,588,580, examiner's answer page 19 first quotation, as well as Ashburn, see page 19 second quotation. The appellant has also argued in the amendment of 2 -27-2002 that conventional wisdom, based upon the Phipps discussion of fully depleting the reservoir

during use, would lead one to do the same concerning fentanyl. This appears to be the reasoning for citing this passage again in part C. of the Appeal brief Summary of the invention. The examiner has cited Lattin et al USPN 5,879,322 and Gale (both discussed above) refuting this allegation. Little discussion if any has been provided in the brief regarding the examiner's rebuttal. The first Phipps declaration also refers to the Kasting article and its transport theory for theoretical membranes. The theoretical discussion discusses theoretical situations of ideal drug behavior in extraneous ion conditions, rather than real observations of drug behavior as in the issue at hand. The first Phipps declaration also references the Padmanabhan et al article and because the threshold value for hydromorphone was found to be of relatively low molarity as opposed to appellant's observations for Fentanyl salt, declarant concludes that this is evidence of non-obviousness. Hydromorphone is completely unrelated in structure, molecular weight and permeability properties. Hydromorphone is disclosed as having passive permeability and because of its chemical composition, does not even need to be converted to a salt form to be used for iontophoresis. There are no parallels in expectations. However, there are parallels in the examiner's arguments and what Padmanabhan shows that is he does perform concentration studies to determine which concentrations are useful for iontophoresis which is the same principle that the examiner has concluded to be obvious. If one follows the teachings of Padmanadabhan one would realize that such concentration studies should be performed with fentanyl salt as well. Finally, the examiner held the first declaration unpersuasive because the passages in the Phipps '894 patent relied upon took this into account. There was no

showing of unobviousness and instead seemed to affirm the need to test fentanyl salt in a similar fashion.

The second Phipps declaration also relied upon unsubstantiated allegations as well, however acknowledges that the examiner is correct concerning the existence of threshold values for medicaments and that the "threshold will likely be dependent on the the physical/chemical properties of the transported species and tissues". As the examiner has been arguing, different thresholds exist for different medicaments based upon their structure. Rebinder expressed this concept concerning complex ions. However, declarant also states that "In addition, the statement in the '894 patent that this threshold value is likely dependent on the physical/chemical properties of the drug species and tissues is also an obvious general principle which is devoid of mechanistic of drug- specific knowledge" which seems to, albeit awkwardly , either reaffirm the examiner's position or state one drug should behave like the next. Obviously no one of any skill in the art would take the later position noting that the 1956 Rebinder article addresses the need for studying complex ions. Declarant then turned the issue to a matter of the magnitude of threshold value observed for fentanyl HCl and suggests it should be considered an unexpected result. If one follows the teachings of Rebinder, Phipps and even Padmanabhan to test various concentrations for the behavior of the admitted known method of treating pain and gets a different value for different drugs this is to be considered an unexpected result? The method taught by the references and admitted in the Jepson claim has the same composition, the tested parameter concentration is the same, and the refernces all teach looking for the same parameter,

that is threshold concentration, and the appellant argues this to be unexpected result? The result that is observed by the secondary references, that drugs have a concentration threshold value is an expected result for all complex drugs including fentanyl salt, however, the magnitude of the value being different amongst different drugs is not necessarily an unexpected result. See the arguments section of the final rejection dated 6-19-02 as well as below discussing what is meant by an unexpected result in the case law and in the MPEP. The examiner does not believe the magnitude to be an regarded as an unexpected result in light of the decisions rendered by the courts. Declarant then criticizes the examiner's understanding of extraneous ions (page 4 of the second declaration) and states that extraneous ions assumed by the examiner to be "if present at the beginning of treatment are still present at the end of treatment" The examiner once again challenges appellant to demonstrate any aqueous solution that does not have extraneous ions at the beginning of use or not end up with ions at the end. As appellant is well aware an aqueous solution of pH 7 has 1 $x10^{-7}$ molar concentration of hydrogen protons that will compete with the drug for delivery. The examiner does not understand the "if present' presumption. Additionally, despite declarant's statements regarding changes in pH not accounted for by the examiner, it is concluded that appellant is also familiar with fact that Haak et al use a combination of Ag/Cl electrodes and Fentanyl HCl drug which helps stabilize the pH at neutral conditions. If anything, declarants statements seem to suggest that perhaps appellant's disclosed invention requires much more narrower conditions than afforded by the scope of the claims. Thus, contrary to appellant's allegations regarding the examiner's

misunderstanding, the examiner is well aware of the principles at hand. Once again the art applied does more to address the "problem" stated in appellant's arguments, than appellant's disclosure and claims. The declarant then concludes that the Kasting model teaches away from his invention because of its teachings in theory. Essentially that one of ordinary skill in the art would blindly follow theory as opposed to empircal testing. Needless to say, in the modernized world, this statement is unpersuasive. Declarant also states that the Haak et al reference in describing the gels, which seem to be fully capable of delivering drugs linearly and at drug fluxes comparable to appellants, have insufficient information to determine the concentration of fentanyl at the end of use. This of course, is not what the examiner has requested information concerning. Rather that whether the gels manufactured have starting concentrations over 16mM which can produce the given fentanyl drug fluxes whenever pain is needed for relief as is stated. The appellant does not appear to be interested in addressing this issue. Of course addressing this issue would require the next consideration of whether that if Haak et al device is designed for multiple dosage delivery as is stated, it would not be obvious for the patient to only uses it once as needed before discarding the remaining contents, Such was known to do as evidenced by Lattin et al USPN 5,879,322.

The examiner has found both Phipps declarations to be off point, unsubstantiated, and unhelpful is determining any distinction and/or unobvious step that may exist the claims as currently presented.

2. Rebuttal to Arguments/Evidence/Affidavits presented in the Appeal Brief - Arguments.

The grouping of claims is no longer required in Appeal briefs but the examiner notes that claim 9 has been argued to be separate because "claim 9 reinforces the distinction over the prior art that they fentanyl delivery from the iontophoretic delivery device should be terminated upon the completion of the total delivery period while a substantial amount of fentanyl remains in the donor reservoir". To be correct appellant really means the fentanyl ion, not fentanyl itself which appellant has been the basis their toxicity arguments. As a sidenote, appellant's arguments would correspond to the following scenario. If one of the references of record teaches multiple dosage deliveries but is capable of being fully depleted of drug during use, and if the patient removes the patch after one dosage application, retaining the 16 mM + conditions, this should be deemed a patentable invention over the method of depleting the reservoir. The examiner does not believe the applied prior art to explicitly teach such a complete reservoir depletion method however, even if it did, would not consider the patient throwing out the patch in it's partially depleted state to be entitled to a new patent.

Turning to appellant's rebuttal, appellant's listing of the prior art beginning at page 9 is noted. The long list of drugs provided in the Phipps'739 patent in the quotation provided is an apparent attempt to show the examiner has involved himself in "picking and choosing" parts of the disclosure. Claim 1 under appeal is a Jepson type claim, the delivery of fentanyl salt by iontophoresis is admitted prior art. The Phipps '739 patent is

cited in the grounds of the rejection merely as formality appreciating the admission and giving one example of how well know it is, that is it is frequently contained in laundry lists in the assignees patents. Admittedly the Haak et al and Thueewes references provide more concise and focused references to the issues at hand.

Appellant's citation of Rebinder passages, however, is a picking and choosing of passages, selecting specific examples rather than what is taught as a whole, namely is the inconsistencies found between delivery and molecules in the past. Appellant does not address the passages relied upon by the examiner or rebut the citations and reasoning behind the rejection

Appellant's comments on Muller, et al is that the reference does not teach fentanyl. The examiner once again reminds appellant that the issue at hand concerns Fentanyl salt. The same may be said for Newman.

Appellant is correct in there assessment of relevant portions of Theeuwes, et al. being the claims, but the prosecution history of the Theeuwes reexam resulting in the reexam certificate offers more detail into the claimed invention.

Part C. of the arguments section provide the substantial portion of the appellant's arguments. The appellant argues that one of ordinary skill in the art would have been inclined to deplete the reservior rather than use it only within the threshold operating range as suggested by the secondary references. Appellant's continued allegations without supporting evidence has long become a reoccurring theme in this file prosecution. The examiner offers rationale within the applied references, cites

references in which fentanyl patches are dispensed while portions remain. See page 20 line 19 to page 21, above of this examiner's answer and the discussion of the Gale 4,588,580 and Lattin et al USPN '322 patents. Why would assignees be inclined to develop patches that were safely disposable as the result of potentially potent remaining portions of potent drugs such as Fentanyl, as taught in the Background of the Lattin patent, if the level of skill at the time of the invention was that alleged by appellant? The examiner notes that those references cited in this argument section and not in the body of the rejections are to establish the level of skill in the art.

In addressing the Phipps declarations the appellant throws out and ignores the references as a whole and latches on to one example and concludes essentially that because Hyrdromorphone has a low threshold level, Fentanyl would be expected to be low as well, even though the drugs and their properties are completely different. Even more so, it would be appellant's logic that there is no need to test Fentanyl. The examiner has presented the Theeuwes patent which claims and covers the delivery of Fentanyl salt for treating pain, the Haak et al patent describing Fentanyl salt for treating a patient by self demand treatment of pain, the discussion in the Padmanabhan article testing hydromorphone and specifically commenting on what drug concentration region is linear and what is not, the Rebinder 1956 article teaching the inconsistencies in results and offering explanation and guidance as to the effects of parasitic ions and how each drug must be tested on its own, the teaching of the inventor himself in his own patents (894)' and the admission in his declaration of recognition of threshold values linearity in delivery, and instead we're going to ignore the years of discussion and

articles and conclude that Fentanyl should behave like Hydromorphone and there is no need or incentive pursue the kinds of test results needed as taught in the prior art. Appellant than moves on *The Gillete Co. v S.C. Johnson* and quotes

> "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desire result, or that the claimed result would be obtained if certain directions were pursued

It is not understood how appellant considers the two references that specifically teach the delivery of fentanyl salt (Theeuwes and Haak et al), for the precise reason as appellant, i.e. to treat patients with pain, to fit the description of a "general disclosure" discussed in Gillette. It is not understood how applicant considers that the references to not discuss the pertinent desired result, threshold value, or how to obtain it. Four references provided Haak et al (column 10 lines 54-59), Rebinder, Phipps and Padmanabhan, show how and why reference linearity is important and how to go about obtaining the threshold value, by testing various concentrations and graphing their results. The Phipps second declaration showed that appellant agrees that this is nothing new. It is beyond the examiner how the Gillette citation can be applied any other possible way but in support of the examiner's position. The references specifically teach the method, the desired result, and the methods how to determine it.

The examiner notes appellant's "new approach" to "parasitic ions" on page 24 and their footnote at the bottom of page 25. Appellant's now contend a position as to what constitutes a "parasitic ion" that will effect drug delivery. Appellant's now allege, once again without any documentation to support their contention, that the "parasitic"

ions responsible are the ones that emerge from the transport of chloride ions from the other side of the epidermis. Apparently, appellant argues that as more chloride ions, which are notably negative in charge, accumulate in the reservoir they will prevent more Fentanyl from being delivered and no other ions are responsible. First of all, the examiner notes that appellant's only demonstration of a threshold value for fentanyl salt being obtained is in figure 2. The results of figure 2 were obtained using a piece of heat stripped cadaver skin placed across the two reservoirs with the counter reservoir containing Dulbecco's phosphate buffered saline (pH 7.4). It appears that appellants sole test results were performed under conditions of unknown chloride concentration (saline) and if appellant's arguments are now taken to be fact, the question arises as to whether the claimed invention only be operable in a threshold region for 16 mM Fentanyl salt when tested in vitro with Delbecco's phosphate buffered saline (pH7.4) of some unspecified salin concentration. The appellant has extrapolated these results to cover the claim as broadly stated in claim 1, which is written to cover in vivo delivery. If appellant's arguments are to be considered fact it raises the question as to how important the value claim is in other conditions, namely of intact skin with epidermis intact. If this is the case, at the results differ, then all criticality for the disclosed invention should be thrown out the door and the examiner's original position that it is obvious to put as much Fentanyl salt in the reservoir as solubility permits. Especially when appellant's only remaining argument is that Fentanyl free base in passive patches can be deadly.

Moreover, following appellants new arguments, even if the concentration of chloride ions is at hand, they would be overwhelmed by the huge amount of Fentanyl concentrations determined to be above threshold as was known to do in the art and which results would have been determined empirically as argued by the examiner. Finally, once again, the examiner's art is better equipped to handle such a situation than what is being claimed by applicant. Haak et al uses silver electrodes along with Fentanyl salt. The reason being, as known in the art, is that silver has a tendency to be oxidized before water. If water is oxidized, as in the case of other electrodes, it forms hydrogen ions in the reservoir which a chief source of competitive ions, contrary to appellants arguments. The positive charged hydrogen ions would compete for transport with the positively charged fentanyl ion, hence the name competitive ions or also known as parasitic ions in the Rebinder reference. However in Haak, it is the silver that is oxidized reacts with chloride ions which quickly precipitate out of solution since they are insoluble in water. Thus, at least the Haak et al reference is equipped to counter choride ions while appellant's claims are not. Past patent have been issued dedicated to this concept and are drawn to reducing competing ions. It doesn't make sense now that appellant would argue that chloride ions and not the hydrogen ions are the problem since the silver electrodes are known to work. The examiner believes that Haak et al reference does more to control parasitic ions than appellant's claims. Appellant's arguments are wholly unpersuasive.

Appellant additionally finds new meaning as to the relative concept of the question"are less drug molecules being moved or more competitive ions?" and states

that this new concept is what the Phipps declaration has been presenting. When iontophoresis is performed, a net total charge of positive ions move out and a corresponding amount of negative ions move in. As less of the drug ions move out, more competitve ions move out to balance the charge. The threshold value is achieved when the drug concentration favor more drug being moved. When the amount of drug ions so overwhelmingly out numbers competitive ions, more drug ions are moved. Appellant takes special notice on page 25 of the brief explaining how that when hydromophone is reduced in reservoirs inorganic competing ions move faster and that net flux of positive ions is comprised of competitive ions rather than the drug. It seems that is the same concept from a different perspective. The examiner is left unimpressed and unpersuaded at this observation as presented by the appellant. The examiner also requests appellant to point out where these arguments have been made before as noted in their footenote at the bottom of page 25 and to point out where in the Phipps declaration appellant draws support. The examiner cannot find it and finds it difficult to track down each and every allegation made by appellant..

Appellant again pursues new obvious to try argument's. The citations of Ex parte Oetiker and In re Kaplan and Ex parte Obukowicz and Merk & Co. Biocraft Laboratories, INC posited earlier by appellant in the response filed 2-27-2002 have apparently been abandoned in light of the examiner's rebuttal beginning at page 24 paragraph 2 of the final rejection mail 6-19-2002. The examiner will represent his arguments below since they seem to support the examiner's position.

The appellant has taken exception to the examiner's contention that the mere determination of fentanyl salt concentration for optimizing efficiency, safety and effectiveness parallels the situation in *In re Hedges* ,783.2d 1038,228 USPQ 685 (Fed. Cir.1986). As in this current application, the examiner in Hedges provided a base reference showing a broad range of that which is claimed and then offered secondary teachings that would suggest and lead to the claimed range. In Hedges, the court found teachings within the references of evidence that directed one of ordinary skill in the art away from the claimed invention. In this application, the only element argued by appellant that teaches away, are his unsubstantiated allegations based upon art that is irrelevant to the claim and rebutted by evidence that is relevant to the claim which has not been addressed by appellant. The examiner contends that board likewise will consider the relevancy of the Hedges citation to be more in line with the examiner's arguments than appellants.

Appellant turns to the *Key Pharmaceutical Inc* decision which the examiner notes that the courts spent substantial time on the evidence and not allegations in rendering their decision. The appellant now have turned to a key issue in the case, that is whether it is obvious to halt delivery, remove the patch and dispose of it while the concentration is still above 16 mM. This of course is what is implied this language is in the claim, but it is not. It just requires stopping the device while there remains a concentration of 16mM or better.The examiner contends that here is where the toxicity of fentanyl HCl may come into effect. Caregivers would not randomly and arbitrarily deliver fentanyl in unknown quantities which would be the case as contended by appellant if the caregiver

were to allow the patient to deplete the reservoir. Because the linear relationship between current and quantity of drug delivered is so critical to be maintained so as to know the amounts delivered, one would not be inclined to deplete the reservoir and deliver an unknown amount. Frequently other drugs are delivered along with patch type medications such as morphine in order to ease pain. The physician would want to know precisely how much is delivered. Appellant in the specification relies upon the patient or the caregiver to control the delivery by patch removal. Although argued in the past that appellant presented a means for stopping the delivery of the medicament, the wording of the specification is at best vague as to how the halting of delivery is done. This became a point of argument which was particularly addressed in rejecting the apparatus claims. Since that time the apparatus claims have been cancelled. No means of automatic termination were disclosed and the board is invited to review those arguments. The current claims would also read upon a patient delivering the medicament only when needed and then disposing of the device.

D. The appellant rebuttal of the Haak et al reference under anticipation. There has been no explicit disputing on behalf of the appellant that the starting concentration but rather the reference teaches stopping delivery when at leat a 16mM concentration exists. The reference states column 10 lines 44+ teaches that device may either me an on-demand, a timer, a fixed or variable resistor a controller that automatically turns the device on and off and that When activated in delivers a fixed amount. The examiner considers this to be instructions on how to use the device. Turning it on and off while delivering a fixed amount. It is noted that one one /off cycle would read upon the claim if

indeed the device is configured to deliver the same amount (i.e. linear operation) each time activated. A control circuit is designed to control the dosage delivered (column 10 lines 60-65) It is noted once again the examiner's art has more structure to complete the task, i.e. an automatic timer than appellants specification or claims. Appellants rebuttal is that one might deplete the reservoir, however this is not taught in the reference and the reference strongly suggests controlling the amount delivered and not delivering outside the constant current range. Appellant's supposition would be a departure from the spirit of the reference when taken s a whole.(column 10 lines 54-59). The secondary references to Haak et al firm the examiner's position on how to determine the linear region. In addition, the patient deciding he only needs one treatment and then disposing of the patch when multiple doses are provided reads upon the claims.

The rejection under Theeuwes has not been rebutted by appellant with any substantial evidence to suggest that Theeuwes would not be operated in the same manner as recited in the claims. The current claims are merely an extension of the method of delivering fentanyl for treating pain

Regarding the double patenting rejection based upon Southam, the examiner again considers the Southam et al claims as another manner of claiming the same invention of treating a patient with fentanyl salt for pain. There is substantial overlap in the method and one would preclude the other.

Finally as noted above, appellant has provide other arguments concerning case law that they have cited. As can be appreciated from the above discussions the appellant believes that an unexpected magnitude in a known result parameter

constitutes an unexpected result. The examiner reproduces the arguments made by the examiner in the final rejection of 6-19-2006 which emphasize this point.

Turning to applicant's citation of case law, applicant first cites In re Oetiker, 24 USPQ 2d 1443 (Fed.Cir.1992) and urges that the prior art must provide some reason, suggestion or motivation found in the prior art that would make the claimed invention obvious. The examiner notes the citation and, contrary to the case of Oetiker, the examiner is not making a non-analogous art combination such as that of a hose clamp and garment fastener in Oetiker. Instead, the examiner combines references that are all concerned with applicant's field of endeavor, that is, the transdermal delivery of drugs by iontophoresis. The applicant also considers the examiner's rejection to be akin to the application of art in the case of Ex parte Obukowicz and urges the same standard of "obvious to try" had been applied based upon a similar generalized statement. The examiner disagrees. In the case of Obukowicz, the examiner applied two references against a claim that required the insertion of a gene encoding a toxin into bacteria and then applying the bacteria to a plant environment to combat plant insects. While the primary reference (Dean) discussed bits and pieces of the claimed invention in separate portions of the text, there is no specific teaching of combining the pieces in a manner which would meet the rejected claims. The board wrote:

> This specific statement regarding combating mosquitos using genetically engineered "natural pond microflora" is relied on by the examiner for the "suggestion" required by the aforementioned case law. However, the specific statement by Dean is not a suggestion to insert the gene into the *chromosome* of bacteria *and* apply that bacteria to the plant environment in order to protect the plant. At best, the Dean statement is

> but an invitation to scientists to explore a new technology that seems a promising field of experimentation The Dean statement is of the type that gives only a general guidance and is not at all specific to the particular form of the claimed invention, and how to achieve it. Such a suggestion may make an approach "obvious to try" but it does not make the invention obvious.

The courts went on to demonstrate with the teachings of other related documents how the Dean statement in the primary reference could have been directed to other inventions such as altering bacteria that grows on a pond surface and that it did not necessarily direct the reader to the invention as claimed by Obukowicz. The "general knowledge" of which the board spoke of in the case of Obukowicz was dealing with general statements that offered little or no direction to result in the claimed invention. In stark contrast, the primary references in each of the current rejections, specifically Theeuwes, Haak and Phipps specifically direct the reader to the claimed invention with the exception of drug concentrations. While the secondary references, namely Rebinder, Muller and Phipps, may be considered to teach "generalized concepts" of applying drugs by iontophoresis in the sense that the are principles that apply to all drugs to be delivered, it is clearly not the same "general knowledge" the board spoke of in Obukowitz and applicant's citation of such are not applicable to the facts concerning the application of art in this application.

Perhaps applicant's citation of Merck & Co. V. Biocraft Laboratories, Inc. , 10USPQ@D 1843,1845 (Fed Cir.1989) is of the most significance since it not only demonstrates applicant's misapplication of case law concerning applicant's third "obvious to try" argument but also directly refutes applicant's fifth argument concerning

the magnitude of concentration in regard to threshold values for fentanyl as opposed to other drugs. In Merck, a question of validity before the court as to whether a commonly owned patent of the Merck Co., USPN 3,313,813 rendered obvious the later obtained 3,781,430 patent which claims a composition of amiloride hydrochloride and hydroclorothiazide with a 1:1 to 1:10 ratio of the drugs respectively. Th earlier '430 patent includes a list of compounds including amiloride and derivatives thereof and later teaches that the are useful in combination with other classes of diuretic agents to prevent the loss of potassium which the reference identifies hydrochlorothiazide as an example. No mention of ratios of the claimed drug composition were disclosed. In determining the ultimate legal conclusion of obvious of the '430 patent over the '813, the court set forth current guidelines regarding "obvious to try" type rejections and how they applied to the Merck litigation.

> [1] An invention is "obvious to try" "where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful". In re O'Farrell, 853 F.2d 894, 903, 7, USPQ2d 1673, 1681 (Fed. Cir. 1988). This is not the situation here. The '813 patent expressly teaches "that when co-administerred with other diuretic agents known to enhance the limitation of potassium ions along with sodium ions the novel pyrazinoylguanidines of this invention will reduce the excretion of potassium ions and thus overcome this undesirable property of other diuretic agents". As is apparent 'success ' is not dependent upon random variation of numerous parameters. On the contrary , the '813 patent instructs the artisan that any of the 1200 disclosed combinations will produce a diuretic formulation with desirable sodium and potassium eliminating properties.

The issue in the Merck case then turns to the magnitude of the results. The examiner considers the arguments advanced in the in the current application to be similar those in Merck. While Rebinder, Muller and the Phipps '894 patent recognized the relationship of extraneous ions and drug concentration, Phipps even in his own declaration acknowledges the principle in the first paragraph

as quoted on page 13. Then Phipps then tries to redefine his invention in terms of the threshold magnitude.

> In contrast, my discovery that fentanyl and sufentanil have a high threshold concentrations could not have been predicted from any statement made in the Padmanabhan article or, for that matter, in the '894 patent.

Essentially, Phipps argues that the magnitude of the results should render the claims nonobvious. A similar argument was raised in Merck to which the court responded.

> But, "absolute predictability of success" is not the criterion; "[f]or obviousness under 103, all that is required is a reasonable expectation of success." In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1681. When further questioned on uncertainty inhered not in the fact that an increase was to be expected, but only in the magnitude of the increase.

To which the courts further added

> The evidence at trial showed that, through requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine.

The examiner considers the current claimed invention to be nothing more than a routine testing of the drug fentanyl. Applicant's have merely taken a conventional gel, added some conventional compounds and experimented on cadaver skin to test which concentrations work best. To emphasize this point the examiner further notes *In re Aller*, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955) to which the Merck decision refers:

> Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances , however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art.

Such is the case in the current application. As noted, applicant himself in his own declaration acknowledged that the realization of the relationship between extraneous ions and drug threshold concentrations were nothing new to the art and attributes his results in figure 1 as to the same

mechanism as that explained in the Phipps '894 patent as well as the Muller and Rebinder references.

> These results show that as the fentanyl HCl concentration falls below about 6 mg/ml, a more significant portion of the applied electrotransport current is carried by ions other than fentanyl ions and the fentanyl flux is more dependent on the fentanyl HCl concentration.

Clearly there was motivation to seek out and discover these values. The examiner adds that In re Antonie, 195 USPQ 6 (CCPA 1977) as cited by applicant in his brief deals with situations in which parameters (specifically the ratio of holding tank volume to contracter area) which were not demonstrated by the examiner to be known optimizable parameters cannot be considered obvious. Such is not the case here.

Finally in regard to applicant's fourth argument as enumerated earlier above which states that the Phipp's '739 patent teaches away from the invention when read in light of the Phipps declaration, like applicant's other arguments simply has no merit. References are taken to mean what they say and are subject to an interpretation by the author filed years later. The evidence of record overwhelming supports the examiner's position and contrary to applicant's statement that the examiner is clinging to a single statement, the prior art demonstrates that applicant did nothing more than test a known system to determine the value of a known parameter. Therefore applicant's arguments are deemed wholly unpersuasive and the examiner maintains the rejections as applied earlier in this office action.

In conclusion, it is the examiner's position that the current pending claims involve nothing more than routine testing to determine the molarity at which Fentanyl should be maintained during delivery so as to maintain a linear relationship between flux and current. The result is a desired one and the secondary references show how to obtain its region through empirical testing. The current claims would merely extend the patent protection obtained long ago by assignees in a way that would be required in order to perform as previously indicated in their patents

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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